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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,060	07/10/2000	Neil Andrew Williams	CTH-03	6761

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,060	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-107,109-113 and 115-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *109-113* is/are allowed.

6)☒ Claim(s) *101-107 and 115-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/06 has been entered.

2. Claims 101-107, 109-113, and 115-124 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 101-107 and 115-124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of treating a subject for an allergic or hypersensitivity condition comprising mucosally administering to the subject an effective amount of an agent selected from the group consisting of EtxB and CtxB that bind to GM1 wherein the agent is co-administered with an allergen and is not coupled to said allergen, (2) the said method wherein the method is a method of treating said subject for asthma, or allergic rhinitis, (3) a method of treating for treating a subject for asthma comprising mucosally administering A method for treating a subject for asthma comprising mucosallv administering to the subject an effective amount of an agent wherein the agent is EtxB that binds to GM1 as set forth in claims 109-113, **does not** reasonably provide enablement for (1) a method for treating a subject for any allergic or hypersensitivity condition comprising mucosally administering to the subject an effective amount of an agent selected from the group consisting of Etx or Ctx that bind to GM1 wherein the agent is co-administered with any allergen or any antigen and is not coupled to said allergen or antigen as set forth in claims 101, 102-104, 115, 117, and 119 (2) a method for treating a subject for an allergic or hypersensitivity condition comprising mucosally administering to the subject an effective amount of EtxB that binds to GM1 wherein the EtxB is co-administered with any antigen and is not coupled to said antigen as set forth in claims 105,

106, 107, 116, 118, 120, (3) A method for treating a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of EtxB that binds to GM1 wherein the EtxB is co-administered with an allergen or antigen and is not coupled to said allergen or antigen, (4) the method for treating a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of EtxB that binds to GM1 wherein the EtxB is co-administered with an allergen or antigen and is not coupled to said allergen or antigen and wherein the agent EtxB is administered intravenously, or intramusculary, (5) the method for treating a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of EtxB that binds to GM1 wherein the EtxB is co-administered with an allergen or antigen and is not coupled to said allergen or antigen and wherein the agent EtxB is administered intravenously, or intramusculary and therein the method is a method for treating asthma, and (6) the method for treating a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of EtxB that binds to GM1 wherein the EtxB is co-administered with an allergen or any antigen and is not coupled to said allergen or antigen and wherein the agent EtxB is administered mucosally, intravenously or intramuscularly and therein the hypersensitivity condition is contact sensitivity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. This rejection encompasses two distinct issues, which will be addressed in turn:

A. Enablement is not commensurate in scope with claimed method for treating allergic or hypersensitivity condition in which Etx or Ctx is administered mucosally with any antigen that is not coupled to said antigen.

The specification discloses a method for screening agents capable of modulating ganglioside-associated activity. The specification asserts that GM1 binding agent such as Ctx and Etx is effective for an allergic condition and/or a hypersensitivity condition wherein the Ctx or EtxB agent is not coupled to an allergen (page 28, line 26-30, page 29). This is because the whole toxin Etx and Ctx also bind with high affinity to GM1 by blocking an IgE mediated response through modulation of a ganglioside associated activity. The specification defines mucosal surfaces includes but is not limited to oral, sublingual, intranasal, vaginal, rectal, salivary, intestinal and conjunctival surfaces.

However, there is insufficient guidance as to the structure of any "antigen" for the claimed method. Further, there is insufficient guidance and in vivo working example showing that the whole Ctx and Etx is effective for an allergic condition and/or a hypersensitivity condition such as asthma, allergic rhinitis.

Snider et al (J Immunology 153: 647-657, 1994; PTO 892) teach antigen such as hen egg white lysozyme HEL or OVA when given orally (mucosally) with CTX whole cholera toxin (CTX) can induce a hypersentivity in the subject and subsequent parenteral challenge with the same antigen would lead to anaphylactic response (see entire document, abstract, page 653, Fig 5, in particular). In contrast, mice immunized orally with similar amount of HEL or OVA either alone or with the B subunit of CTX (CTB) did not resulted in sensitization (see page 653, col. 2, in particular).

Marinaro et al (J Immunology 155: 4621-4629, 1995; PTO 892) teach antigen such as hen egg white lysozyme HEL or OVA when given orally (mucosally) with CTX whole cholera toxin (CTX) can induce antigen specific IgE, and IgG1, a Th2 type immune response (see page 4627, col. 2, page 4623, col. 2, CT-induce IgE, in particular).

Post filing date reference Hirai et al (Microbiol Immunol 44(4): 259-66, 2000; PTO 892) conclude that co-administration of allergen such as Japanese cedar pollen with cholera toxin (CT) intra-nasally induces pollen-specific allergic state in mice (see abstract, in particular). Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed method for treating allergic or hypersensitivity condition in which Etx or Ctx is administered mucosally with any antigen.

B. Enablement is not commensurate in scope with claimed method for treating asthma in which EtxB is administered intravenously or intramuscularly with any antigen that is not coupled

to said antigen. This is because immunomodulation by EtxB and allergen depends on the *route* of administration and the structure of the allergen or antigen.

Takabayashi et al (J Immunology 170: 3898-3905, 2003; PTO 892) teach the induction of mucosal immunity generally requires local antigen exposure. Takabayashi et al teach only intranasal administration of allergen such as OVA protects against allergic hypersensitivity responses in the airways such as asthma and allergic rhinitis (see page 3904, in particular).

Wiedermann *et al,* of record, teach suppressive versus stimulatory effects of allergen/cholera toxoid (CtB) conjugates depending on the nature of the allergen in which murine model of type I allergy as well as the route of administration (See abstract, in particular). In particular, cholera toxin when administered simultaneously with an antigen by the mucosal route, it enhances immune response to the co-administered antigen (see page 1132, col. 1 first paragraph, in particular). In contrast, mucosal administration of B subunit of cholera toxin (CTB) physically coupled to an antigen enhances peripheral tolerance induction (see page 1132, col. 1, first paragraph, in particular).

Kagan *et al*, of record, teach presently, the only available treatment of food allergies is dietary vigilance and administration of self-injectable epinephrine (abstract, in particular).

Herz *et al*, of record, teach allergens can differ in their immunogenicity as well as in their capacity to act as tolerogens (See abstract, page 274, nature of the antigen, in particular). Herz *et al* teach until now no mouse model has been available which resembles all of human bronchial asthma (page 272, column 2, Animal models of type I allergy and asthma, in particular). Each individual mouse strain demonstrates a unique response pattern following immunization of allergens. The same allergen causes different phenotype dependent on genetical prerequisites (page 273, column 1, in particular). Further, the route of allergen administration has important impact on the quality of the immune response (See page 273, column 2, in particular). Herz et al teach that dependence of experimental model and the antigen used, the effects as well as the mechanisms of action can vary which might indicate the complexity of predicting clinical consequences of any therapeutic approach (see page 279, in particular).

Tamura et al, of record, teach that the *physical association* of LTB and antigen such as OVA is required to mediate immune suppression (See page 228, column 1, Figure 2, in particular).

Hoynes et al, of record, teach that allergic sensitization is a Th2 process where Th2 T helper cells are more efficient in secreting IL-4, IL-5, and IL6 which promote the growth and

differentiation of B cells and induce isotype class switching toward IgG1 and IgE in human (see page 180, col. 1, in particular). Hoynes et al teach successful treatment of allergy is accompanied by a *decrease* in Th2-type cytokine production and a concomitant switch to Th1 immune response (see page 180, col. 2, in particular).

Williams et al, of record, teach that co-administering ExtB agent that binds to GM1 not couple to antigen such as collagen type II (CII) to DBA mice *increases* IL-4 (Th2 immune response) with a concomitant reduction in interferon gamma (Th1 immune response) (see abstract, page 5291, Materials and methods, col. 2, first paragraph, in particular). Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/27/06 and the declaration by Neil Williams have been fully considered but are not found persuasive.

Applicants' position is that the declaration by Neil Williams filed December 16, 2002 provided enabling data relating to use of EtxB in studies of animal allergic response modeling human airway diseases. The newly submitted declaration filed 2/27/06 answered the question of the "effective amount" of Ctx, Etx, CtxB and EtxB to be coadministered with the allergen/antigen, and of the route of administration that is effective for the claimed method. It is respectfully submitted that the newly submitted declaration answers both these questions, as it provides enabling data of what is an "effective amount" when used in mucosal administration in accordance with the method of the invention in mice. A person of ordinary skill in the art could readily determine the "effective amount" in humans and other mammals. Further, in the declaration it is specified that the effective amount is administered mucosally, and most specifically by intranasal administration.

In response to the argument that the effective amount of the agent is administered mucosally, claim 122 still recites the agent is administered intravenously, intramuscularly or subcutaneously for treating asthma (claim 123).

As evident by the teachings of Takabayashi et al (J Immunology 170: 3898-3905, 2003; PTO 892) that induction of mucosal immunity generally requires local antigen exposure. Takabayashi et al teach only intranasal administration of allergen such as OVA protects against allergic hypersensitivity responses in the airways such as asthma and allergic rhinitis (see page 3904, in particular). Wiedermann *et al,* of record, teach suppressive versus stimulatory effects of allergen/cholera toxoid (CtB) conjugates depending on the nature of the allergen in which murine model of type I allergy as well as the route of administration (See abstract, in particular). In particular, cholera toxin when administered simultaneously with an antigen by the mucosal route, it enhances immune response to the co-administered antigen (see page 1132, col. 1 first paragraph, in particular). In contrast, mucosal administration of B subunit of cholera toxin (CTB) physically coupled to an antigen enhances peripheral tolerance induction (see page 1132, col. 1, first paragraph, in particular).

In response to the argument that the newly submitted declaration provides data to the enablement of the use of Ctx and Etx for the claimed method, it is noted that the data provides enablement for only subunit B of the toxin, such as EtxB is effective for treatment of allergic or hypersensitivity when coadministered intranasally. Treatment with EtxB or EtxB + OVA suppressed the levels of IL-4 in BAL (FIG 4). None of the data provide the use of whole Etx or Ctx. As evident by the teachings of Snider et al (J Immunology 153: 647-657, 1994; PTO 892) that antigen such as hen egg white lysozyme HEL or OVA when given orally (mucosally) with CTX whole cholera toxin (CTX) can induce a hypersentivity in the subject and subsequent parenteral challenge with the same antigen would lead to anaphylactic response (see entire document, abstract, page 653, Fig 5, in particular). In contrast, mice immunized orally with similar amount of HEL or OVA either alone or with the B subunit of CTX (CTB) did not resulted in sensitization (see page 653, col. 2, in particular).

Marinaro et al (J Immunology 155: 4621-4629, 1995; PTO 892) teach antigen such as hen egg white lysozyme HEL or OVA when given orally (mucosally) with CTX whole cholera toxin (CTX) can induce antigen specific IgE, and IgG1, a Th2 type immune response (see page 4627, col. 2, page 4623, col. 2, CT-induce IgE, in particular).

Post filing date reference Hirai et al (Microbiol Immunol 44(4): 259-66, 2000; PTO 892) conclude that co-administration of allergen such as Japanese cedar pollen with cholera toxin (CT) intra-nasally induces pollen-specific allergic state in mice (see abstract, in particular). Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed method for treating allergic or hypersensitivity condition in which the whole toxin Etx or Ctx is administered mucosally with any antigen.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 101, 103, 115, and 117 are rejected under 35 U.S.C. 102(b) as being anticipated by Snider et al (J Immunology 153: 647-657, 1994; PTO 892) as evident by Marinaro et al (J Immunology 155: 4621-4629, 1999; PTO 892).

Snider et al teach a method of treating a subject such as mouse for an allergic or hypersensitivity condition by administering orally to the subject an effective amount of CtxB and antigen such as hen egg lysozyme HEL (see page 652, Figure 2, CTB + HEL, page 648, co. 1, Materials and Methods, in particular). The Snider et al teach mice immunized with CTB and HEL had no significant IgG1 or IgA antibody response and does not potentiate allergic sensitivity in mice to that are sensitized with the allergen. The reference CTB binds to mono-sialoganglioside (GM1) as evidence by the teachings of Marinaro et al (page 4621, col. 1, in particular). Thus, the reference teachings anticipate the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 101, 103, 115, and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,681,571 in view of Snider et al Snider et al (J Immunology 153: 647-657, 1994; PTO 892).

The '571 patent teaches a method for treating a subject such as mice for an allergic or hypersensitivity condition. The reference comprises orally administered to the mice B subunit of cholera toxin (CTB) coupled to an antigen such as sheep red blood cell (SRBC) (see col. 13, lines 55-65, in particular). The reference CTB binds to GM (see col. 1, line 53-55, in particular).

The claimed invention differs from the teachings of the reference only in that the method of treating delayed type hypersensitivity condition wherein the EtxB is not coupled to the antigen, instead of coupled to the antigen.

Snider et al teach administering orally to the subject such as mice an effective amount of CtxB not coupled to an antigen such as hen egg lysozyme HEL (see page 652, Figure 2, CTB + HEL, page 648, co. 1, Materials and Methods, in particular). The Snider et al teach mice immunized with CTB and HEL had no significant IgG1 or IgA antibody response but decreases the amount of histamine release (see Fig. 4, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cholera toxin (CTB) coupled to SRBC for a method of treating hypersensitivity as taught by the '571 patent for the CtxB uncoupled to allergen Ova as taught by Snider et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because co-administration of CtxB with allergen or antigen decreases the amount of histamine release to allergen/antigen in subject that has been sensitized to the allergen/antigen and would not induce

IgE antibody response associated with delayed type hypersensitivity since it has no effect on the IgG1 or IgA antibody response as taught by Snider et al. Further, the unconjugated cholera toxin (CTB) is obvious variation of the teaching of the '571 patent. Claims 102-104, 115, 117, and 119 are included in this rejection because asthma, allergic rhinitis, atopic eczema, dermatitis, uticaria or hives or poison ivy are part of the contact delayed type hypersentivity reactions as taught by the '571 patent.

10. Claims 109-113 are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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